REMARKS

In response to the Office Action mailed July 25, 2008, in connection with the above-identified application, Applicants respectfully request entry of the amended claims and the following remarks. Claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 are pending and under consideration.

Regarding the Amendment to the Specification

The specification has been amended to insert a trademark designation for "TAXOL." Thus, the amendment was made to address an informality. As such, no new matter has been added and entry thereof is respectfully requested.

Regarding the Claim Amendments

The amendments to the claims are supported throughout the specification or were made to address various informalities. In particular, the amendment to claim 21 to recite a heavy chain variable region "that includes amino acids 99-108 of SEQ ID NO:5" is supported, for example, at page 3, lines 5-12, at page 10, lines 5-11, at page 14, lines 5-12, and at page 48, line 19, to page 49, line 7. The amendment to claims 21, 27 and 96 to recite that the antibody or functional fragment thereof "specifically binds to an epitope of an antigen expressed by at least one of" the recited cell lines, and "wherein NORM-2 antibody produced by a cell line deposited as DSM ACC 2626 specifically binds to said epitope of the antigen expressed by at least one of" the recited cell lines is supported, for example, at page 1, lines 27-28, which discloses "a class of polypeptides which react with epitopes specific for neoplastic cells," at page 18, lines 22-25, which discloses "two monoclonal antibodies (NORM-1 and NORM-2),....that specifically recognize a number of carcinomas," and at page 19, lines 1-3, which discloses "the NORM-1 and NORM-2 antibodies, and other antibodies, or fragments thereof, that are specific for the antigen recognized by these antibodies." The amendment to claims 21, 27 and 96 to recite "Colo-699 (DSMZ Accession Number ACC 196), CACO-2 (DSMZ Accession Number ACC169, ATCC Accession Number HTB-37), 23132/87 (DSMZ Accession Number ACC 201), DU-145 (DSMZ Accession Number ACC 261, ATCC Accession Number HTB-81), and BM 1604 (DSMZ Accession Number ACC 298) cells," is supported, for example, at page 13, lines 19-28, and page 51, lines 22-23. The amendment to claims 21 and 29 to delete reference to "an adenocarcinoma of the colon, a diffuse-type stomach carcinoma, an adenocarcinoma of the pancreas, or an adenocarcinoma of the lung" was made in view of the foregoing amendment

reciting the various cell lines. The amendment to claim 30 to delete the recitation of certain cell lines was made in order to differentiate claim 30 from claims 21 and 27. The amendment to claim 47 to replace "polypeptide" with "antibody" was made to provide adequate antecedent basis. Thus, as the claim amendments are supported throughout the specification or were made to address various informalities, no new matter has been added and entry thereof is respectfully requested.

I. REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The rejection of claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 under 35 U.S.C. §112, second paragraph as allegedly indefinite is respectfully traversed. Allegedly the claims are indefinite in the recitation of "functional fragment." Claim 47 is allegedly unclear in reciting "polypeptide."

Claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 are clear and definite. In this regard, each of independent claims 21, 27 and 96 recite that the antibody or "functional fragment thereof specifically binds to an epitope of an antigen ...." Thus, the skilled artisan would know that the recited function is binding. Claim 47 has been amended to recite "antibody" in order to provide adequate antecedent basis. Accordingly, claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 are clear and definite and Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

II. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH, ENABLEMENT

The rejection of claims 30, 47, 93 and 94 under 35 U.S.C. §112, first paragraph as allegedly lacking enablement is respectfully traversed. According to the Patent Office, allegedly it is unclear of the cell lines recited in the claims to which the antibodies or functional fragments may bind are publicly known. In terms of claim 47, it allegedly is unclear if the NORM-2 cell line is publicly available.

Claims 30, 47, 93 and 94 are adequately enabled under 35 U.S.C. §112, first paragraph. In terms of the Colo-699 (DSMZ Accession Number ACC 196), CACO-2 (DSMZ Accession Number ACC169, ATCC Accession Number HTB-37), 23132/87 (DSMZ Accession Number ACC 201), DU-145 (DSMZ Accession Number ACC 261, ATCC Accession Number HTB-81), and BM 1604 (DSMZ Accession Number ACC 298) cell lines, each of these cells lines is available to the public from DSMZ. As evidence of availability, submitted herewith are the relevant pages from the DSMZ catalog and a material transfer

agreement to order these cell lines from DSMZ. (Exhibit E). In particular, Colo-699, Caco-2, 23132/87, Du-145, and Bm 1604 cell lines are listed in the catalog (Exhibit E). Accordingly, as each cell line is publicly available, the ground for rejection under 35 U.S.C. §112, first paragraph must be withdrawn.

In terms of public availability of NORM-2 cell line as represented by DSM ACC2626, Applicants will provide the requisite deposit assurances according to 37 CFR 1.801-1.809 upon notification of allowable subject matter. In the interim, Applicants respectfully note that due to the proprietary nature of the deposit it would be premature to make such assurances prior to notification of allowable subject matter.

The rejection of claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 under 35 U.S.C. §112, first paragraph as allegedly lacking enablement is respectfully traversed. According to the Patent Office, allegedly it would require undue experimentation to make and use the claimed invention.

The proper standard for enablement under 35 U.S.C. §112, is whether one skilled in the art could make and use the invention without undue experimentation. In this regard, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands* 858 F.2d 731, 737 (Fed. Cir. 1988).

Here, in view of the guidance in the specification and knowledge and skill in the art concerning antibody structure and function at the time of the invention, and that antibody variants having the requisite activity could be produced and identified using routine methods disclosed in the specification or that were known in the art at the time of the invention, one skilled in the art could make antibodies and functional fragments that specifically bind to the recited epitope of the antigen without undue experimentation.

First, the level of knowledge and skill in the art with respect to antibody structure correlating with function at the time of the invention was high. For example, the role of antibody heavy and light chain variable regions, particularly CDRs and FRs, in antigen binding were well understood by the skilled artisan at the time of the invention. The specification also discloses the role of antibody heavy and light chain variable regions, including CDR and FR regions, in antigen binding (page 19, line 11, to page 20, line 15). Consequently, in view of the high level of knowledge and skill in the art with respect to

antibody structure correlating with function at the time of the invention clearly the skilled artisan would be apprised of antibody regions that participate in antigen binding and structure.

Second, in addition to the high level of knowledge and skill in the art concerning antibody structure and function, the specification discloses the predicted locations of the CDRs in SEQ ID NOs:5 and 7 (page 3, lines 9-12 and 15-19). In particular, the specification discloses the sequences of the predicted CDRs in SEQ ID NOs:5 and 7 in Figures 9 and 10. Furthermore, in view of the fact that the specification discloses the location of the CDRs in SEQ ID NOs:5 and 7 and that SEQ ID NOs:5 and 7 are human sequences, the skilled artisan would know the predicted location of the FRs in SEQ ID NOs:5 and 7, which flank the CDRs. Consequently, the skilled artisan would know the predicted location of CDRs and FRs of SEQ ID NOs:5 and 7.

Third, because the knowledge and skill in the art at the time of the invention was high in terms of antibody structure correlating with function, and the location of sequences in SEQ ID NOs:5 and 7 that contribute to antigen binding and structure are disclosed, the skilled artisan would also know residues in SEQ ID NOs:5 and 7 amenable to substitution and therefore, be able to predict with reasonable certainty variants of SEQ ID NOs:5 and 7 that would have at least partial antigen binding activity. For example, the skilled artisan would know that an amino acid substitution, such as a conservative substitution, for example, outside of or within a CDR or FR region of in SEQ ID NOs:5 and 7 would likely not destroy antigen binding activity. In addition, the skilled artisan knows that antibody FRs and CDRs can tolerate substitutions.

To corroborate that substitutions within CDRs are tolerated, submitted herewith as Exhibit A is a publication by Kipriyanov et al. (Protein Engineering 10:445 (1997)). In Exhibit A the authors report that a substitution of a cysteine residue by a serine within CDR3 of an antibody heavy chain variable region did not have an adverse effect on affinity. Thus, Exhibit A corroborates that CDRs tolerate amino acid substitutions.

To corroborate that substitutions within FRs are tolerated, submitted herewith as Exhibit B is a publication by Holmes *et al.* (J. Immunol. 167:296 (2001)). The authors of Exhibit B report several heavy chain variable region FR substitutions of an anti-lysozyme antibody did not destroy binding activity. Thus, Exhibit B corroborates that FRs tolerate substitutions.

To corroborate that insertions and deletions of amino acid residues in heavy and light chain variable regions, including CDRs, are tolerated submitted herewith as Exhibit C is a publication by Wilson *et al.* (J. Exp. Med. 187:59 (1998)). The authors of Exhibit C report a number of insertions and deletions of variable heavy chains that occur naturally during affinity maturation which are tolerated. Thus, Exhibit C corroborates that heavy and light chain variable regions tolerate insertions and deletions.

To further corroborate that insertions and deletions of amino acid residues in heavy and light chain variable regions, including CDRs, are tolerated submitted herewith as Exhibit D is a publication by Lantto and Ohlin (J. Biol. Chem. 277:45108 (2002)). The authors of Exhibit D report that single amino acid insertions or deletions of CDRs 1 and 2 of heavy chain variable region of an antibody were well tolerated. Thus, Exhibit D corroborates that heavy or light chain variable region sequences tolerate insertions and deletions, even within a CDRs.

Consequently, in view of the guidance in the specification and the high level of knowledge and skill in the art regarding antibody structure and function, the skilled artisan would know of general regions and particular residues that would be more or less amenable to substitution and could therefore predict SEQ ID NOs:5 and 7 variants likely to have at least partial antigen binding activity without actually having to produce such variants and fragments. Given the large number of amino residues in variable regions, clearly many variants of SEQ ID NOs:5 and 7 could be readily produced without undue experimentation that have at least partial antigen binding activity.

Fourth, the level of knowledge and skill in the art regarding making antibodies and antigen binding fragments thereof was also high. For example, methods of producing antibodies and variants without undue experimentation are disclosed in the specification (page 23, line 14, to page 26, line 19) and were also known in the art at the time of the invention. Methods of producing antibody fragments (*e.g.*, Fv, Fab, Fab' and $F(ab')_2$) were known in the art and were routine at the time of the invention. Methods of identifying antibody variants and fragments that bind antigen without undue experimentation were also known in the art and are taught by the specification. In particular, routine methods for measuring antibody binding to antigen or cell lines, as well as methods for measuring cell proliferation and apoptosis are disclosed in the specification (page 44, line 9 to page 45, line 19; page 49, line 10, to page 54, line 14). Thus, in view of the guidance in the specification and the high level of knowledge and skill in the art at the time of the invention, one skilled in

the art could readily make antibodies and functional fragments that specifically bind to the recited antigen without undue experimentation.

Analogous to *In re Wands,* 858 F.2d 731 (Fed. Cir. 1988), where the court held that screening hybridomas to determine those that produced monoclonal antibodies having a particular binding characteristic did not require undue experimentation, undue experimentation would not be required to produce antibodies and functional fragments that bind to the recited antigen, given that 1) producing antibody variants and fragments was routine; and 2) cell binding, antibody competition, proliferation and apoptosis assays were routine in the art at the time of the invention. Thus, contrary to the assertion in the Office Action (pages 24 -25) where it is stated that one skilled in the art essentially would have to "predict in advance" the sequence of antibodies that would bind in order to produce the claimed antibodies and functional fragments, there is no need for the skilled artisan to "predict" in advance variants or fragments that bind to the recited antigen in order to make variants and functional fragments because making antibodies and functional fragments and screening for those having binding activity was routine and well established at the time of the invention. In this regard, case law has never required that enablement under 35 U.S.C. §112, first paragraph be demonstrated by a particular mode or methodology, i.e., the ability to "predict in advance" the antibodies having binding activity. Here, in view of the guidance in the specification and knowledge in the art at the time of the invention, the skilled artisan could readily produce and identify antibody variants and functional fragments of SEQ ID NO:5 and 7 without any advance knowledge of the effect of particular substitutions, insertions or deletions on activity without undue experimentation. Consequently, one skilled in the art need not analyze nor need to predict with certainty the effect of any substitution, insertion or deletion *a priori* in order to satisfy enablement under 35 U.S.C. §112, first paragraph.

In view of the foregoing, the skilled artisan could make antibody variants and functional fragments as claimed without undue experimentation. Consequently, claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 are adequately enabled under 35 U.S.C. §112, first paragraph, and Applicants respectfully request that the rejection be withdrawn.

III. REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The rejection of claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 under 35 U.S.C. §112, first paragraph as allegedly lacking adequate written description is respectfully traversed. According to the Patent Office, allegedly the skilled artisan would not be reasonably apprised that Applicants had possession of the claimed invention.

Claims 21 to 23, 27 to 32, 35, 47 and 89 to 96, prior to entry of the present amendments are adequately described by the originally filed specification. Nevertheless, solely in order to further prosecution of the application and without acquiescing to the propriety of the rejection, have been amended as set forth above. The rejection will therefore be addressed as if applied to the amend claims upon entry of this response.

Applicants first respectfully point out that the "Guidelines for Examination of Patent Applications...." cited in the Action at page 6 are merely that, namely guidelines. The "Guidelines" are not statutory nor judicial authority. Consequently, Applicants will refrain from addressing any grounds for rejection based upon the aforementioned "Guidelines."

Secondly, much of the cited case law is not pertinent to claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 since in contrast to these claims, these cases did not concern the written description requirement, or concerned claims directed to compounds for which there was either no structure described, or little if any knowledge of correlation between structure and function. For example, in *University of Rochester v. Searle*, 358 F.3d 916 Fed. Cir. 2004. In *Rochester*, the patent at issue claimed methods of using Cox-2 inhibitors for pain and inflammation control. However, in the *Rochester* patent at issue there was not a single example of a Cox-2 inhibitor disclosed. Furthermore, in the *Rochester* patent at issue there was no guidance concerning the structure of a Cox-2 inhibitor. In stark contrast to the facts in *Rochester*, the specification discloses a structure, that of an antibody, whose structure and function were well known to the skilled artisan at the time of the invention. Furthermore, the specification discloses a working example of an antibody. Moreover, the specification discloses the location of amino acid sequences of antibody light and heavy chain variable regions that contribute to antigen binding and maintaining antibody structure. Consequently, the facts of the claimed subject matter are clearly distinguishable from *Rochester* for at least these reasons.

In Enzo Biochem, Inc v. Gen-Probe Inc., 296 F3d 1316 (Fed. Cir. 2002) the court stated "it is insufficient to define a substance solely by its principal property;" however, none

of claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 describe the antibodies and functional fragments "solely by its principal biological property." In *Amgen v. Chugai Pharmaceutical*, 927 F.2d 1200 (Fed. Cir. 1991), written description was not at issue.

In *Noelle v. Lederman*, 355 F.3d 1343 (Fed. Cir. 2004), the Applicant claimed an antibody that binds to human CD40CR based upon the sole disclosure of a mouse CD40CR- there were no human CD40CR characteristics provided. In *University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997), the Applicants claimed "vertebrate insulin cDNA" and "mammalian insulin cDNA" based upon the sole disclosure of a rat cDNA- there were no common characteristics provided to define such an insulin genus. However, in contrast to both *Noelle* and *Lilly*, the claimed antibodies and functional fragments bind to an antigen expressed by at least one of Colo-699 (DSMZ Accession Number ACC 196), CACO-2 (DSMZ Accession Number ACC169, ATCC Accession Number HTB-37), 23132/87 (DSMZ Accession Number ACC 201), DU-145 (DSMZ Accession Number ACC 261, ATCC Accession Number HTB-81), and BM 1604 (DSMZ Accession Number ACC 298) cells. Furthermore, the claimed antibodies and functional fragments bind to the epitope of the antigen to which antibody produced by a cell line deposited as DSM ACC 2626 binds. Moreover, as described in detail below, the heavy and light chain variable regions of the claimed antibodies and functional fragments share significant sequence homology (at least 80%) with heavy and light chain variable region sequences SEQ ID NOs:5 and 7. Additionally, the claimed antibodies and functional fragments include a heavy chain variable region with all of the amino acids (99-108) of the predicted CDR3 of SEQ ID NO:5. Still further, the specification provides guidance concerning sequence regions that correlate with function, and there was significant knowledge concerning correlation of antibody structure and function at the time of the invention. Consequently, the facts of the claimed subject matter are clearly distinguishable from the facts of both *Noelle* and *Lilly* for at least these reasons.

The written description requirement under 35 U.S.C. §112, first paragraph is "to clearly convey the information that an applicant has invented the subject matter which is claimed." *In re Barker*, F.2d 588, 592 (CCPA 1977). A proper analysis for written description under 35 U.S.C. §112, first paragraph is whether one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991); see, also, *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985). Possession is assessed from

the viewpoint of one of ordinary skill in the art: "Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). The description needed to satisfy the requirements of 35 U.S.C. §112 "varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence.....Since the law is applied to each invention in view of the state of the relevant knowledge, its application will vary with differences in the state of the knowledge in the field and differences in the predictability of the science....the law must take cognizance of the scientific facts." *Capon v. Eshhar*, 418 F.3d , 1349, 1357 (Fed. Cir. 2005). Thus, an adequate written description is a factual inquiry measured by one of ordinary skill in the art, that varies with the nature and scope of the invention, taking into consideration the scientific and technologic knowledge in existence in the relevant field.

Furthermore, to satisfy the written description requirement, "Applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." *In re Angstadt*, 537 F.2d 498, 502-503 (CCPA 1976), *Utter v. Hiraga*, 845 F.2d 993, 998-99 (Fed. Cir. 1988). In this regard, "(1) examples are not necessary to support adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner v. Inglis*, 448 F.3d 1357 (Fed. Cir. 2006). Thus, in view of the standard set by the court, an actual reduction to practice or disclosure of specific examples of antibodies or functional fragments within the scope of the claims is clearly not required to satisfy written description under 35 U.S.C. §112, first paragraph.

Turning to the facts of claims 21 to 23, 27 to 32, 35, 47 and 89 to 96, as discussed above the skilled artisan has substantial understanding of antibody structure and function. The specification also teaches antibody heavy and light chain variable region sequences (e.g., SEQ ID NOs:5 and 7) having binding activity within the genus. The specification further teaches the predicted positions of the three CDRs in each heavy and light chain variable region sequence, and therefore the position of the flanking regions (FR). In view of the foregoing guidance, one skilled in the art would know the location of the amino acid sequences that contribute to antigen binding and antibody structure.

As also discussed above, the level of knowledge and skill in the art with respect to antibody structure and function correlations was high at the time of the invention. Evidence

of such knowledge, such as native antibodies having two heavy and light chain sequence, the presence and contribution of three CDRs to binding, and the role of FRs is disclosed in the specification. Thus, in view of the high degree of knowledge and skill in the art concerning antibody structure and function at the time of the invention, when combined with the guidance of the specification of the heavy and light chain variable sequences, SEQ ID NOs:5 and 7, the location of the CDRs and FRs that contribute to antigen binding, the cells types expressing the antigen, and the high degree of sequence identity to SEQ ID NOs:5 or 7, the skilled artisan would know variants of SEQ ID NOs:5 and 7 that would retain at least partial antigen binding activity Consequently, the skilled artisan would be apprised of a number of antibodies and functional fragments within the scope of the claims.

Furthermore, the claimed antibodies and functional fragments heavy and light chain variable regions share significant sequence homology (at least 80%) with heavy and light chain variable region sequences SEQ ID NOs:5 and 7. Moreover, the claimed antibodies and functional fragments include a heavy chain variable region with all of the amino acids (99-108) of the predicted CDR3 of SEQ ID NO:5. Consequently, given the well understood correlation between antibody structure and function, that the antibodies and functional fragments share significant sequence homology (at least 80%) to SEQ ID NOs:5 and 7, that the heavy chain variable region of the antibodies and functional fragments include all of the amino acids (99-108) of the predicted CDR3 of SEQ ID NO:5, and that the specification discloses an embodiment within the genus having binding activity, clearly the claims meet the written description standard under 35 U.S.C. §112, first paragraph.

In sum, the claimed antibodies and functional fragments are described 1) structurally- they have heavy and light chain variable region sequences with at least 80% identity to SEQ ID NOs:5 and 7, and the heavy chain variable region includes all of the amino acids (99-108) of the predicted CDR3 of SEQ ID NO:5; and 2) functionally- they bind to an antigen expressed by at least one of Colo-699 (DSMZ Accession Number ACC 196), CACO-2 (DSMZ Accession Number ACC169, ATCC Accession Number HTB-37), 23132/87 (DSMZ Accession Number ACC 201), DU-145 (DSMZ Accession Number ACC 261, ATCC Accession Number HTB-81), and BM 1604 (DSMZ Accession Number ACC 298) cells. Thus, the claimed antibodies and functional fragments are described both structurally and functionally.

In terms of the concern in the Office Action (e.g., page 10) regarding a description of the antigen to which the antibodies bind, as discussed above the antigen is defined based

upon its binding to antibody produced by a cell line deposited as DSM ACC 262. The antigen is also defined in terms of types of cell lines that express the antigen (i.e., at least one of Colo-699 (DSMZ Accession Number ACC 196), CACO-2 (DSMZ Accession Number ACC169, ATCC Accession Number HTB-37), 23132/87 (DSMZ Accession Number ACC 201), DU-145 (DSMZ Accession Number ACC 261, ATCC Accession Number HTB-81), and BM 1604 (DSMZ Accession Number ACC 298) cells). Thus, the antigen is described in terms of the antibody that the antigen binds and cell type expression.

Furthermore, where one of skill in the art would be apprised of the antibodies and functional fragments having binding activity there is no need to identify or sequence the antigen. Here, in view of the guidance in the specification and the substantial knowledge concerning correlation of antibody structure and function known in the art at the time of the invention, clearly one of skill in the art could envision antibodies and functional fragments having binding activity. Furthermore, the antigen is expressed by at least one of Colo-699 (DSMZ Accession Number ACC 196), CACO-2 (DSMZ Accession Number ACC169, ATCC Accession Number HTB-37), 23132/87 (DSMZ Accession Number ACC 201), DU-145 (DSMZ Accession Number ACC 261, ATCC Accession Number HTB-81), and BM 1604 (DSMZ Accession Number ACC 298) cells. Moreover, the antigen binds to the antibody produced by a cell line deposited as DSM ACC 262. Consequently, given the foregoing knowledge, there is no need to isolate or sequence the antigen in order for one skilled in the art to know antibodies and functional fragments that bind to the antigen.

Finally, the issue of whether a single species of polypeptide provides an adequate written description for a genus of polypeptides was recently decided in *Invitrogen Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052 (Fed. Cir. 2005). The facts concerning the claimed antibodies and functional fragments are remarkably similar to *Invitrogen*. In *Invitrogen* the court held that a single embodiment of a protein (a reverse transcriptase (RT)) provided an adequate written description of claims directed to a genus of such proteins. The court reasoned that the single disclosed protein embodiment was adequate to satisfy the written description requirement of 35 U.S.C. §112, first paragraph because the protein had 1) sufficient correlation between structure and function; and 2) shared significant homology with others. In affirming that the patents in-issue satisfied the written description requirement, as articulated by the court in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (1997) and *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993), the court held that "the shared written description for the patents-in-issue recites both the DNA and

amino acid sequences of a representative embodiment of the claimed RT enzyme. The specification also discloses test data that the enzyme produced by the listed sequence has the claimed features—DNA polymerase activity without RNase H activity. Under both the *Eli Lilly* and *Fiers* analysis, the specification at bar is sufficient. In short, there is no error in the district court's ruling that the claims in the patents-in-suit satisfy the written description requirement of §112." Thus, even with a single disclosed embodiment, the claims of the patents in-issue in *Invitrogen*, which were not limited by reciting a particular amount of homology or identity to a reference sequence, were held to satisfy the written description requirement for the genus. Accordingly, in view of *Invitrogen* a single embodiment provides a written description for a genus of proteins where there is sufficient correlation between protein structure and function, and the members of the species share significant homology. Here, for the reasons articulated herein, clearly there is sufficient correlation between antibody structure and function, and the members of the antibody species share significant homology with each other.

In sum, in view of the guidance in the specification and the substantial understanding of antibody structure and function correlations at the time of the invention, the significant degree of sequence identity of the claimed antibodies and functional fragments to SEQ ID NOs:5 and 7, the skilled artisan would be apprised of a number of antibodies and functional fragments of claims 21 to 23, 27 to 32, 35, 47 and 89 to 96. Furthermore, in view of the substantial understanding of the correlation of antibody structure and function, the significant sequence identity of the species required by the claims, and that the specification discloses an embodiment having binding activity, clearly the claims meet the standard for written description articulated by the court in *Invitrogen*. Consequently, claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 are adequately described under 35 U.S.C. §112, first paragraph, and Applicants respectfully request that the rejection be withdrawn.

The rejection of claims 21 to 23, 28 to 32, 35, 47 and 89 to 95 under 35 U.S.C. §112, first paragraph as allegedly lacking adequate written description is respectfully traversed. According to the Patent Office, the recitation of "an adenocarcinoma of the colon, a diffuse-type stomach carcinoma, an adenocarcinoma of the pancreas, or an adenocarcinoma of the lung" in the claims allegedly is new matter.

As discussed above, the written description requirement under 35 U.S.C. §112, first paragraph is "to clearly convey the information that an applicant has invented the subject

matter which is claimed." *In re Barker*, F.2d 588, 592 (CCPA 1977). Possession is assessed from the viewpoint of one of ordinary skill in the art: "Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). Notably, the courts have never required that the subject matter of the claims be described literally or using the same terms- there is no "*in haec verba*" requirement

Claims 21 to 23, 28 to 32, 35, 47 and 89 to 95, prior to entry of the present amendments are adequately supported by the originally filed specification. Nevertheless, solely in order to further prosecution of the application and without acquiescing to the propriety of the rejection, have been amended as set forth above. The rejection will therefore be addressed as if applied to the amend claims upon entry of this response.

In particular, claims 21 to 23, 28 to 32, 35, 47 and 89 to 95 have been amended to delete the recitation of binding to "an adenocarcinoma of the colon, a diffuse-type stomach carcinoma, an adenocarcinoma of the pancreas, or an adenocarcinoma of the lung." Consequently, the ground for rejection is moot. Applicants further note that as set forth above support in the specification for binding to the various cell types and cell lines does not require "not binding to non-neoplastic cells." Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, written description be withdrawn.

IV. REJECTIONS UNDER 35 U.S.C. §102

The rejection of claims 21, 27, 30, 31, 32, 47 and 95 under 35 U.S.C. §102(b), as allegedly anticipated by Immunobiology 5 (Janeway et al. pp 96-7 (2001), as evidenced by Kettunen (C. Gen. Cyto. 149:98 (2004)) is respectfully traversed. According to the Patent Office, allegedly the reference describes each and every element of claims 21, 27, 30, 31, 32, 47 and 95.

Claims 21, 27, 30, 31, 32, 47 and 95 are neither taught nor suggested by the cited references. In particular, the claims require, *inter alia*, binding to an epitope of an antigen expressed by at least one of Colo-699 (DSMZ Accession Number ACC 196), CACO-2 (DSMZ Accession Number ACC169, ATCC Accession Number HTB-37), 23132/87 (DSMZ Accession Number ACC 201), DU-145 (DSMZ Accession Number ACC 261, ATCC Accession Number HTB-81), and BM 1604 (DSMZ Accession Number ACC 298) cells. In contrast, neither of the cited references alone, or in combination, teach or suggest an antibody or functional fragment thereof that binds to an epitope of an antigen expressed by at least one

of Colo-699 (DSMZ Accession Number ACC 196), CACO-2 (DSMZ Accession Number ACC169, ATCC Accession Number HTB-37), 23132/87 (DSMZ Accession Number ACC 201), DU-145 (DSMZ Accession Number ACC 261, ATCC Accession Number HTB-81), and BM 1604 (DSMZ Accession Number ACC 298) cells. Consequently, claims 21, 27, 30, 31, 32, 47 and 95 are not anticipated by Immunobiology 5 (Janeway et al. pp 96-7 (2001) alone, or in combination with Kettunen (C. Gen. Cyto. 149:98 (2004)) and Applicants respectfully request that the rejection under 35 U.S.C. §102(b) in view of Immunobiology 5 (Janeway et al. pp 96-7 (2001), as evidenced by Kettunen (C. Gen. Cyto. 149:98 (2004)) be withdrawn.

The rejection of claims 21 to 23, 27 to 31, 35, 47 and 89 to 96 under 35 U.S.C. §102(b), as allegedly anticipated by Vollmers et al. (Cell 40:547 (1985)) is respectfully traversed. According to the Patent Office, allegedly the cited reference describes each and every element of claims 21 to 23, 27 to 31, 35, 47 and 89 to 96.

Claims 21 to 23, 27 to 31, 35, 47 and 89 to 96 are neither taught nor suggested by the cited reference. Nevertheless, solely in order to further prosecution of the application and without acquiescing to the propriety of the rejection, the claims have been amended as set forth above. The rejection will therefore be addressed as if applied to the amend claims upon entry of this response.

As a first issue, Applicants respectfully point out that a reference cited under 35 U.S.C. §102 must have an enabling disclosure. However, claims 21 to 23, 27 to 31, 35, 47 and 89 to 96 have also been rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enablement. Consequently, the rejections are contradictory: if the claims lack enablement under 35 U.S.C. §112, then the claims cannot also be rejected under 35 U.S.C. §102 since Vollmers et al. must be an enabling disclosure to properly be cited against the claims; if, on the other hand the claims are rejected under 35 U.S.C. §102, then they must be enabled and then the claims cannot also be rejected under 35 U.S.C. §112 as lacking enablement. Applicants therefore request withdrawal of either the rejection under 35 U.S.C. §112 or the rejection under 35 U.S.C. §102 as they cannot be maintained simultaneously against claims 21 to 23, 27 to 31, 35, 47 and 89 to 96.

As a second issue, as discussed above for the rejection to be proper Vollmers et al. must enable one of skill in the art at the time of the invention to make the claimed antibodies and functional fragments without undue experimentation. However, at best Vollmers et al.

mention an antibody by the same name as disclosed in the specification, NORM-2. However, there is no sequence information for NORM-2 (or any antibody for that matter) in Vollmers et al. Furthermore, there is no deposit or other information for NORM-2 (or any antibody for that matter) in Vollmers et al. indicating that the antibody is publicly available. Absent such information, one of skill in the art would have been unable to obtain any antibody without undue experimentation, let alone the antibody or functional fragment of any of claims 21 to 23, 27 to 31, 35, 47 or 89 to 96.

In view of the foregoing, Vollmers et al. (Cell 40:547 (1985)) fail to enable claims 21 to 23, 27 to 31, 35, 47 and 89 to 96. Accordingly, the rejection under 35 U.S.C. §102(b) in view of Vollmers et al. (Cell 40:547 (1985)) is improper and must be withdrawn.

The rejection of claims 21 to 23, 27 to 31, 35, 47 and 89 to 96 under 35 U.S.C. §102(a), as allegedly anticipated by Brandlein et al. (Cancer Res. 63:7995 (2003)) is respectfully traversed. According to the Patent Office, allegedly the cited reference describes each and every element of claims 21 to 23, 27 to 31, 35, 47 and 89 to 96.

Claims 21 to 23, 27 to 31, 35, 47 and 89 to 96 are neither taught nor suggested by the cited reference. Nevertheless, solely in order to further prosecution of the application and without acquiescing to the propriety of the rejection, the claims have been amended as set forth above. The rejection will therefore be addressed as if applied to the amend claims upon entry of this response.

The subject application claims priority to USSN 60/519,550, filed November 12, 2003. In contrast, the publication date of Brandlein et al. (Cancer Res. 63:7995 (2003)) as indicated on the first page (upper left hand corner) is November 15, 2003. Consequently, Brandlein et al. (Cancer Res. 63:7995 (2003)) is not prior art against claims 21 to 23, 27 to 31, 35, 47 and 89 to 96. Accordingly, the rejection under 35 U.S.C. §102(a) in view of Brandlein et al. (Cancer Res. 63:7995 (2003)) is improper and must be withdrawn.

The rejection of claims 21 to 23, 30 to 32, 89, 90 and 92 to 95 under 35 U.S.C. §102(e), as allegedly anticipated by Babcock et al. (US Patent No. 7,285,269) is respectfully traversed. According to the Patent Office, allegedly the cited reference describes each and every element of claims 21 to 23, 30 to 32, 89, 90 and 92 to 95.

Claims 21 to 23, 30 to 32, 89, 90 and 92 to 95 are neither taught nor suggested by the cited patent. Nevertheless, solely in order to further prosecution of the application and

without acquiescing to the propricty of the rejection, the claims have been amended as set forth above. The rejection will therefore be addressed as if applied to the amend claims upon entry of this response.

The amended claims are directed to isolated antibodies and functional fragments thereof which, among other things, the heavy chain variable region includes amino acids 99-108 of SEQ ID NO:5. In contrast, Babcock et al. fail to teach or suggest an antibody with a heavy chain variable region that includes amino acids 99-108 of SEQ ID NO:5. In particular, for example, at least two residues in amino acids 99-108 of SEQ ID NO:5, namely positions 99 and 100, which are Alanine and Leucine, respectively, are distinct from any heavy chain variable region described in Babcock et al.

Furthermore, the antibody described by Babcock et al. is stated to bind to TNF alpha. In contrast, the claimed antibodies and functional fragments do not bind to TNF alpha, rather they bind to an epitope of an antigen expressed by at least one of the recited cells, wherein antibody produced by a cell line deposited as DSM ACC 2626 specifically binds to the epitope of the antigen.

As evidence that the claimed antibodies and functional fragments do not bind to TNF alpha, submitted herewith as Exhibit F is data indicating that NORM-2 antibody does not detectably bind to TNF alpha. In brief, two SDS-Page Gels (12%) were loaded with pure TNF alpha (abcam: ab9642, recombinant TNF alpha, human) and lysates of A549, HeLa and MKN cells. Both gels were blotted on nitrocellulose membranes. One membrane (Exhibit F, left panel) was stained with anti TNF alpha (abcam: ab9809, mouse monoclonal [NF-7] to human TNF alpha, immunogen was recombinant human full length protein) and with rabbit anti mouse IgG HRP (Dako: P0161). The TNF alpha signal (17 kDa) is clearly visible (arrow). The other membrane (Exhibit F, right panel) was stained with human IgM NORM-2 and with rabbit anti human IgM HRP (Dako: P0215). NORM-2 did not detectably stain TNF alpha (Exhibit F, right panel). Accordingly, NORM-2 does not detectably bind to TNF alpha. Consequently, the claimed antibodies and functional fragments also do not detectably bind to TNF alpha.

In sum, as Babcock et al. fail to describe an antibody or functional fragment thereof with a heavy chain variable region that includes amino acids 99-108 of SEQ ID NO:5, and describe antibodies that bind to TNF alpha, whereas the claimed antibodies and functional fragments do not detectably bind to TNF alpha, the claimed antibodies and functional fragments are neither taught nor suggested by Babcock et al. Accordingly, the rejection under

35 U.S.C. §102(e) in view of Babcock et al. (US Patent No. 7,285,269) is improper and must be withdrawn.

CONCLUSION

Please charge any fees associated with the submission of this paper to Deposit Account Number 033975. The Commissioner for Patents is also authorized to credit any over payments to the above-referenced Deposit Account.

Respectfully submitted,

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